CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20738/S001

MEDICAL REVIEW(S)

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Medical Review

NDA #: 20-738/SE2-001
Drug Name: eprosartan
Type of Document: efficacy supplement
Medical Reviewer: Charles J. Ganley, M.D.

Volume: 26.1
Sponsor: SmithKline Beecham
Correspondence Date: 2/3/98
Date Completed: 9/11/98

The sponsor has submitted revised labeling for eprosartan partially based on new information in study 124 (reviewed by Dr. Stockbridge). There are additional clarifications of safety data (reviewed by Dr. Gordon). The attached label has been marked with reference letters. The following table lists the reference letters on the labeling with comments pertinent to each reference letter.

Reference Letter	Comment
A	Changes are acceptable.
B	Changes are not acceptable. 1) The change was based on an active control study that suggests a response rate of 66% with a single agent. This response rate exceeds the response rate of the mild, moderate hypertension trials. 2) The change could suggest that control of blood pressure with a single agent is likely in patients with severe hypertension. This message should not be conveyed. 3) There is limited data available in severe hypertension.
C	All of the changes are acceptable except for the addition of the word '....and one study comparing .....should be .....and one study comparing). This was a dose titration study which is an inadequate design to directly compare two dose regimens.
D	Changes are acceptable.
E	Changes are not acceptable. The changes proposed by the sponsor completely change the message to be conveyed (i.e. the trough peak effect with once a day dosing is attenuated compared to BID dosing).
F	Changes are not acceptable. The information provided does not support the change. The same data that Dr. Temple reviewed is listed as the supporting data.
G	Changes are not acceptable. The information provided does not support the change. The same data that Dr. Temple reviewed is listed as the supporting data.
H	Changes are acceptable.
I	Changes are not acceptable. None of the changes proposed are acceptable. There should be no distinction between controlled trials and open label trials. Based on Dr. Gordon's review, ~~five~~ two patients were withdrawn due to increased creatinine and BUN and three for increased creatinine only.
J	Changes are not acceptable. None of the changes proposed are acceptable. There should be no distinction between controlled trials and open label trials. Based on Dr. Gordon's review, two patients were withdrawn due increased liver funtion tests.
K	Changes are not acceptable. None of the changes proposed are acceptable. There should be no distinction between controlled trials and open label trials. Based on Dr. Gordon's review, two patients were withdrawn due to anemia.
L	Changes are not acceptable. None of the changes proposed are acceptable. There should be no distinction between controlled trials and open label trials.
M	Changes are acceptable.
N	Changes are not acceptable. None of the changes proposed are acceptable. There should be no distinction between controlled trials and open label trials. Based on Dr. Gordon's review, four patients withdrew due to thrombocytopenia.

O	Changes are not acceptable. None of the changes proposed are acceptable. There should be no distinction between controlled trials and open label trials. Based on Dr. Gordon's review, one patient withdrew due to hyperkalemia and three with hypokalemia.
P	Changes are not acceptable. Replace first paragraph with: The usual recommended starting dose of Tevetan is 600 mg once daily when used as monotherapy in patients who are not volume depleted (See WARNINGS, Hypotension in Volume-and/or Salt-Depleted Patients). Tevetan can be administered once or twice daily with total daily doses ranging from 400 mg to 800 mg. There is limited experience with doses beyond 800 mg/day. If the anti-hypertensive effect measured at trough using once-daily dosing is inadequate, a twice-a-day regimen at the same total daily dose or an increase in dose may give a more satisfactory response. A diuretic may be added if blood pressure is still not adequately controlled, but there is no experience with doses above 400 mg twice daily in combination with a diuretic. Achievement of maximum blood pressure reduction in most patients may take 2 to 3 weeks. This change incorporates labeling similar to the labeling of candesartan and losartan.

The sponsor also proposed changing the Geriatric Use section (see reference letter G). Dr. Temple wrote the original section based on his interpretation of the data in the original NDA. The data has not changed so it seems unreasonable that the interpretation of the data should change. The change in the Geriatric Use section proposed by the sponsor sends a very different message compared to the current labeling. The changes proposed by the sponsor to the Geriatric Use section are not acceptable.

/S/

Charles J. Ganley, M.D.

cc: orig.
HFD-110
HFD-110 / CSO / C. GANLEY

JUN 24 1998

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Joint Clinical Review

NDA: 20-738

Sponsor: SmithKline Beecham

Submission: SE-001 (January 26, 1998): a request to approve eprosartan for once-daily administration in the treatment of mild-to-moderate essential hypertension.

Review date: June 24, 1998

Reviewers: W. Nuri, Ph.D.,HFD-710 /S/

N. Stockbridge, M.D., Ph.D., HFD-110 /S/

Concurrence: K. Mahjoob, Ph.D., HFD-710 /S/

G. Chi, Ph.D., HFD-710 /S/ FOR /S/

Summary: This is a review of Study 124, a randomized, parallel, 8-week comparison of placebo and once-daily eprosartan 600 mg in the treatment of mild-to-moderate essential hypertension. The study was conducted and submitted to support a change in the recommended dosing instructions from twice-daily only to once- or twice daily. Although the trial was marred by problems with some centers, the overall result plausibly supports such a change in labeling.

Distribution: NDA 20-738
HFD-110/Project Manager
HFD-710/Nuri
HFD-110/Stockbridge
HFD-710/Mahjoob
HFD-710/Chi
HFD-110/Gordon

1 Study 124: A double-blind, placebo-controlled, multicenter study of efficacy and safety of oral eprosartan (600 mg) taken once daily in patients with essential hypertension (DBP ≥95 and ≤114 mmHg).

1.1 Source documents Study protocol NDA 20-738, vol 2.012; study report vol 2.001; electronic document: none; SAS datasets.

1.2 Investigators Multi-center study with 31 investigators in the United States.

1.3 Study dates 21 July 1997 to 10 November 1997.

1.4 Study design **Source.** This study description was based upon the protocol dated 2 July 1997[1].

Supplies. Drug supplies are shown in Table 1. The eprosartan formulation is the same as that approved for marketing.

Table 1. Drug supplies (Study 124).

	Lot		Lot
Placebo 300 mg	U96304	Eprosartan 300 mg	U96306

Subjects. Enrollment criteria were conventional. The intent was to randomize 220 male and female subjects of low child-bearing potential, age >18, with essential hypertension characterized as average DBP between 95 and 114 mmHg at three regularly-scheduled run-in visits, with the difference between the highest and lowest such values ≤12 mmHg and the difference in the last two such values ≤8 mmHg. Subjects were excluded for:

Risks to attribution
- Pregnancy, lactation
- Advanced retinopathy
- Ventricular tachycardia requiring treatment
- MI or stroke within 90 days
- CHF requiring banned drug
- Angina requiring banned drug
- Unstable diabetes
- Renal or hepatic disease
- Survival-limiting disease
- Sensitivity to related drugs

Population-defining
- Sitting SBP>200 mmHg
- Hypertension secondary to contraceptives
- Other secondary hypertension

Risks to compliance
- Alcohol or drug abuse

Disallowed drugs
- ACE inhibitors
- Diuretics
- Regular nitrates
- β-blockers
- Calcium channel blockers
- Recent investigational drugs
- Sympathomimetic amines
- NSAIDs
- MAO inhibitors
- Tricyclic antidepressants
- Phenothiazines
- Prior eprosartan

[1] The study was originally designed with 3 arms. The third arm was dropped and associated changes were made, but no amendments appear to have been implemented after enrollment began.

Procedure. The trial procedure was conventional. Subjects underwent a 3- to 5-week single-blind, placebo-withdrawal period with biweekly assessment of blood pressure. Eligible subjects were evenly randomized to placebo or eprosartan 600 mg and followed at two-week intervals for 8 weeks. Conventional advice was given concerning the manner of blood pressure measurement; each day's reported value was the mean of 3 measurements. Study drug was to be taken in the morning; no specific relationship to food is mentioned.

End point. This trial had higher discriminatory power than is usual. The primary end point was the trough sitting diastolic blood pressure, with the last observation carried forward to week 8. The sample size was chosen to provide 90% power to detect a 3.5-mmHg change in sitting DBP (double-difference from baseline and placebo), with p=0.05. No interim analysis was planned.

Safety. Safety monitoring was adequate. Baseline physical examination, laboratory analyses, ECG, and pregnancy testing were performed at an initial screening visit. End-of-treatment assessments were performed at the end of week 8. Subjects returned 5 to 7 days after their last dose for a final physical exam, ECG, and laboratory tests. Subjects were withdrawn for mean sitting DBP >120 mmHg on any visit, sitting DBP >115 mmHg for 2 visits, or sitting SBP >200 mmHg for 2 visits.

1.5 Results

1.5.1 Conduct

Enrollment. Three hundred and twenty-eight subjects were screened and entered single-blind run-in, 243 were randomized, and 206 (85%) completed study. Individual sites enrolled 3 to 20 subjects.

Demographics. Treatment groups were similar. Demographics of the 2 treatment groups are shown in Table 2. Treatment groups were similar with respect to history of prior treatment for hypertension and for sitting diastolic pressure at baseline.

Table 2. Demographics (Study 124).

		Placebo N=120	Eprosartan N=123			Placebo N=120	Eprosartan N=123
Age	<65 (%)	85	85	Race (%)	Caucasian	68	76
	≥65 (%)	15	15		Black	18	15
	Mean±SEM	53±1	54±1		Oriental	4	0
Sex	Male (%)	63	58		Other	9	9
	Female (%)	37	42	Weight	Mean±SEM	90±2	91±2

Withdrawal. Eighty-one percent of subjects on placebo completed 8 weeks of double-blind treatment, versus 89% on eprosartan. Reasons for discontinuation are summarized in Table 3.

Table 3. Disposition of subjects (Study 124).

	Placebo N=120	Eprosartan N=123
Completed	97	109
Withdrew	23	14
Adverse event	9	3
Lack of effectiveness	8	6
Loss to follow-up	2	1
Protocol violation	0	3
Other	4	0

Protocol violations. No protocol violations excluded subjects from the sponsor's analyses of effectiveness. Four subjects at one center received study drug for the same randomization code for 7 to 16 days; three of them subsequently were withdrawn for lack

of compliance and the fourth subject was withdrawn for lack of effectiveness. None of these subjects has a post-baseline assessment of blood pressure[2]. Four subjects at another center were randomized in the wrong order, but the blind is believed intact and these subjects contribute to the analysis of effectiveness.

1.5.2 Effectiveness

Detailed procedure. The sponsor's analysis technique was reasonable. They performed a last-observation-carried-forward analysis of the intent-to-treat population; i.e., any subject with at least one post-baseline assessment of effectiveness. The sponsor treated the mean of the last two qualifying measurements as the baseline. The analysis of variance included terms for center, treatment, and treatment-by-center; if $p>0.1$ for treatment-by-center, this term was dropped from the model.

The reviewers' analyses were similar.

The sponsor's analysis for the primary end point is shown in Table 4. This result was obtained after dropping the treatment-by-center interaction term; the results with the term are not materially different.

Table 4. Mean±SEM trough sitting DBP and SBP (Study 124).

	DBP		SBP	
	Placebo N=118	Epro N=119	Placebo N=118	Epro N=119
Baseline	101.2±0.4	100.4±0.4	150.5±1.1	149.4±1.1
End point	99.3±0.8	92.9±0.9	151.3±1.6	143.5±1.7
Change	-1.7±0.7	-7.5±0.8	0.8±1.2	-6.0±1.3
Double difference	-5.6		-6.8	

The sponsor also performed an analysis of variance comparing the treatment groups by visit, using SAS/GLM. The results of this analysis are shown in Table 5.

Table 5. Least-squares means±SEM trough sitting DBP and SBP (Study 124).

	DBP		SBP	
	Placebo N=118	Epro N=119	Placebo N=118	Epro N=119
Change	-1.5±0.8	-7.6±0.8	0.9±1.3	-6.6±1.3
Double difference	-6.1		-7.5	

[2] It is unclear how a subject with no assessment post-baseline could be withdrawn for lack of effectiveness.

The sponsor's analyses of treatment by subgroups for age, gender, race, and prior treatment did not find a significant interaction, but the treatment-by-center interaction was statistically significant, with the magnitude of treatment effect varying by center as illustrated in Figure 1.

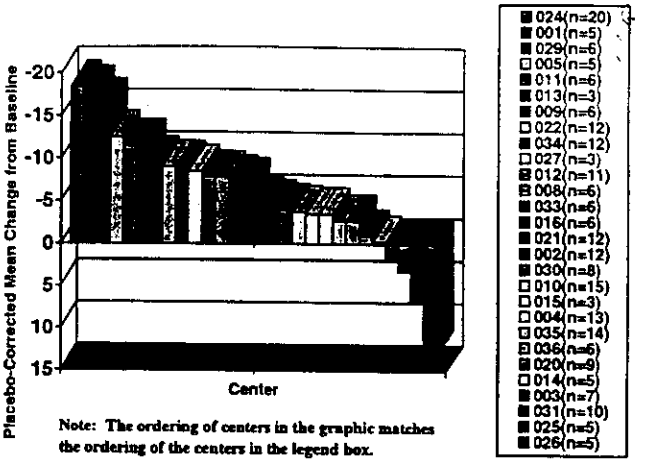

Figure 1. Treatment effect size by center (Study 124).

Heterogeneity of results by center led the reviewers to further characterize the changes in vital signs as follows. Measurements of heart rate, diastolic pressure, and systolic pressure, sitting and standing were all treated the same, without regard to differences in units. For each visit day, the "change in vital sign" (ΔVS) was calculated as the difference from the first to the second and from the second to the third measurements. Examples of the distributions of ΔVS

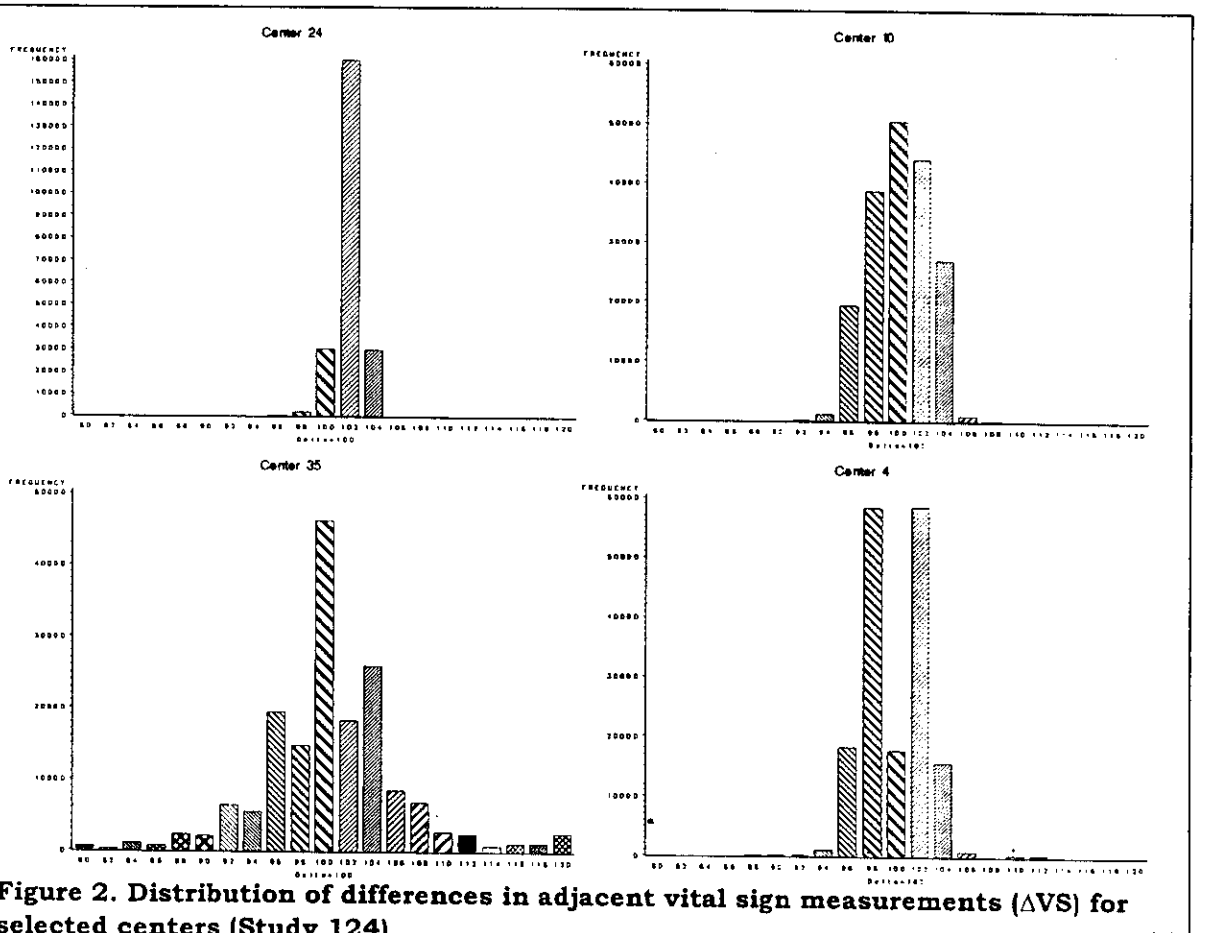

Figure 2. Distribution of differences in adjacent vital sign measurements (ΔVS) for selected centers (Study 124).

are displayed for the 4 largest centers in Figure 2[3].

One center appears to be an outlier in Figure 2 (and among the full set of 31 centers). At this center, by a wide margin, it was most common for the second or third vital sign measurement to be exactly 2 units lower than the preceding measurement. Fewer than 1% of second or third measurements were higher than the preceding measurement. Statistical properties of the distributions of ΔVS are shown in Figure 3. Center 24, with the largest number of subjects and the largest number of measurements of vital signs, also has the smallest observed variance and standard deviation.

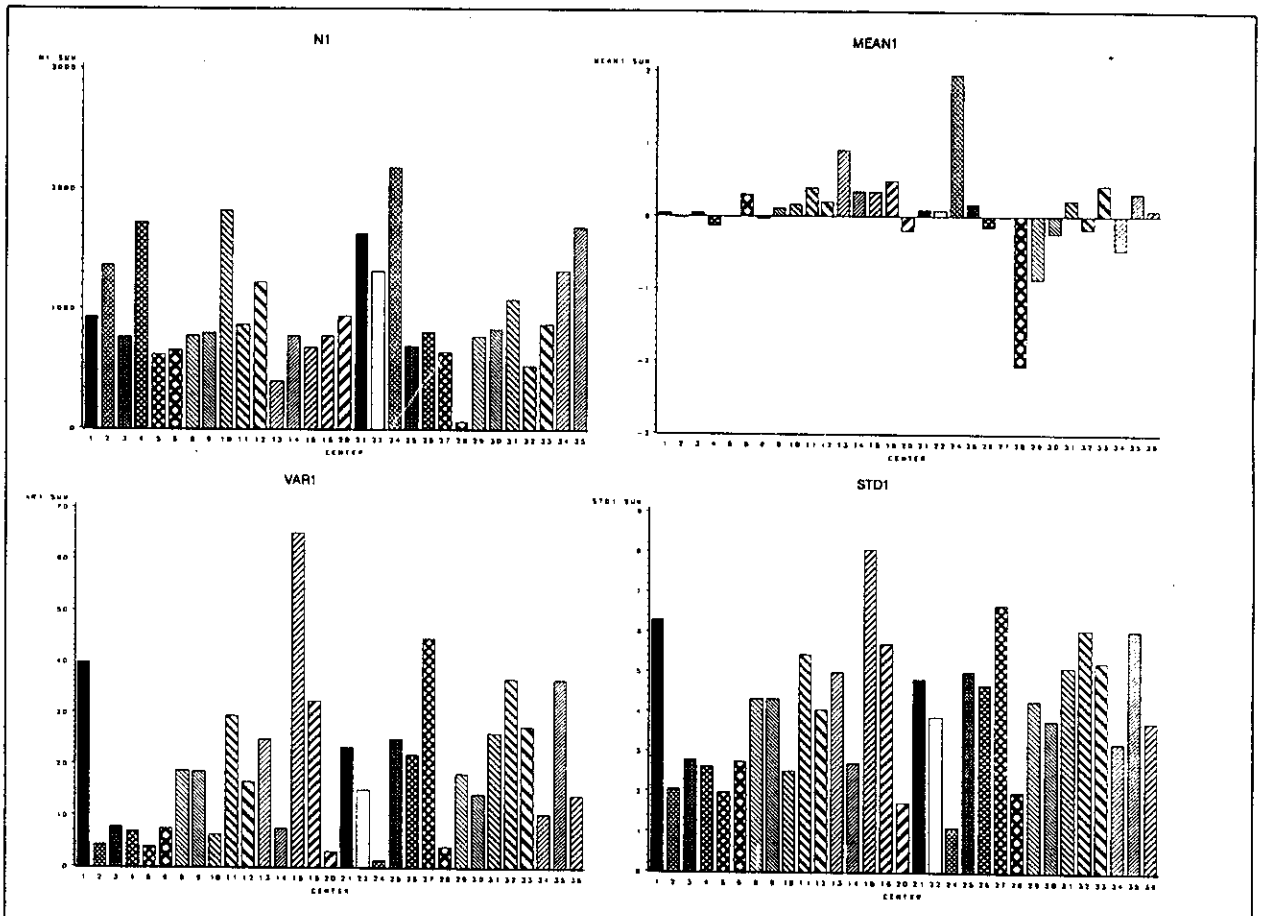

Figure 3. Count (N), mean, standard deviation, and variance for the distribution of changes in adjacent measurements of vital signs (ΔVS), by center (Study 124).

[3] What is plotted in Figure 2 is a histogram of 100+(measurement 1) – (measurement 2) or 100+(measurement 2) – (measurement 3), to cope with an idiosyncrasy of the SAS/Graph procedure.

The distribution of ΔVS for center 24 is truncated. This is shown in Figure 4, a plot of the range of ΔVS as a function of the number of values (N). Center 24 has the largest number of observations and the smallest observed range.

The distribution of ΔVS for center 24 is skewed. Fewer than 1% of the values for this center were negative[4].

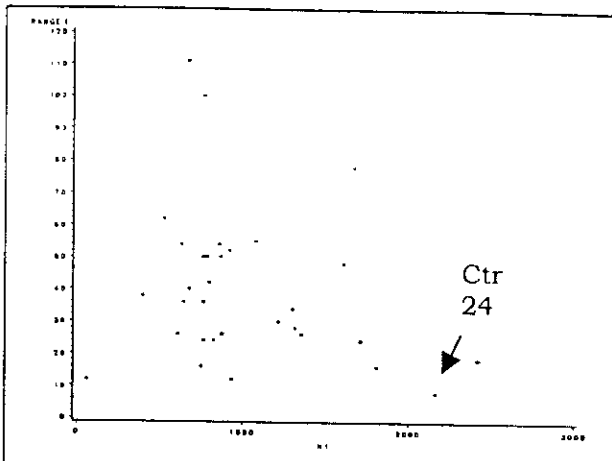

Figure 4. Range of ΔVS by the number of observations (Study 124).

Thus, the vital sign data from center 24 display numerous unusual features:

- The small placebo effect can possibly be attributed to the racial composition of the subjects at this center.
- However, this same characteristic (a mostly Black population) makes the observed treatment effect size--largest of any center--less plausible. This raises a question about whether the blind was intact.
- The change from the first to the second and from the second to the third measurement in any vital sign obtained sitting or standing on any visit date displayed highly unlikely characteristics--a very narrow distribution skewed toward progressively declining values.

These unusual features in the data for center 24 warrant investigation by DSI. However, no other center's data appear to have similar characteristics, so the impact of excluding only 8% of subjects enrolled at center 24 has a modest effect on the main study findings. The reviewers tested this assertion by sequentially dropping from the analysis centers in the order of decreasing magnitude of treatment effect, as shown in Table 6. The 7 centers with the largest treatment effect can be dropped from the analysis and preserve $p<0.05$.

Table 6. Effect of dropping centers from primary end point analysis (Study 124).

Excluded centers	N	*P*-value for	
		Treatment Effect	Treatment X center
None	237	<0.0001	0.022
24 only	217	0.0001	0.24
24, 1, 29, 5, 11, 13, 9	186	0.035	0.54
24, 1, 29, 5, 11, 13, 9, 22	174	0.079	0.49
24, 1, 29, 5, 11, 13, 9, 22, 34	162	0.15	0.61

[4] A negative value would mean, for example, that the value on measurement 2 was *greater* than the value at measurement 1.

Time course. The time course of development of effects on diastolic pressure (double-differences from baseline and placebo) is shown in Figure 5 (sponsor's analysis, reviewers' figure). The results suggest that most of the effect develops within 2 weeks.

Subgroups. The sponsor's analyses of effects in age subgroups are shown in Table 7. Similar analyses were conducted by the sponsor on subgroups by sex (somewhat larger effects in women), race (somewhat larger effects in Blacks[5]), and baseline sitting diastolic blood pressure (somewhat larger effects with baseline <105 mmHg). These analyses were not redone by the reviewers.

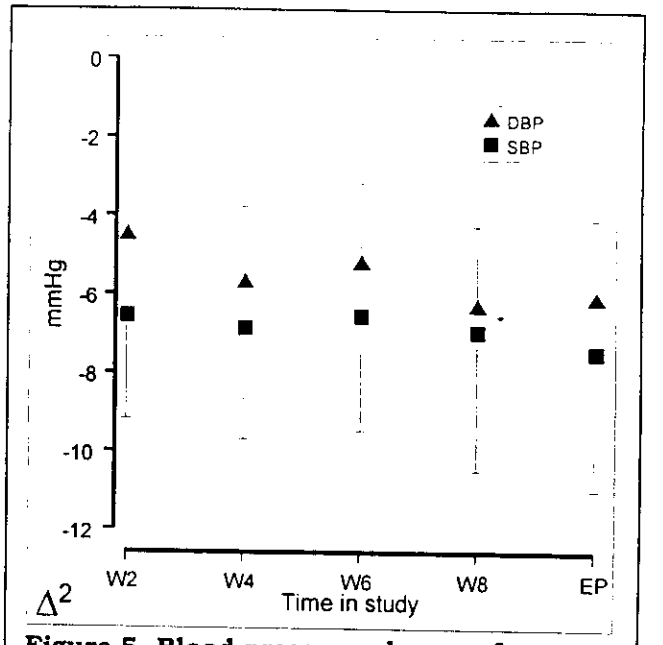

Figure 5. Blood pressure changes from baseline and placebo, by time (Study 124).

Table 7. Mean±SEM trough sitting DBP and SBP by age (Study 124).

	DBP				SBP			
	Age <65		Age ≥65		Age <65		Age ≥65	
	Placebo N=101	Epro N=102	Placebo N=17	Epro N=17	Placebo N=101	Epro N=102	Placebo N=17	Epro N=17
Baseline	102±0.4	101±0.4	100±1.0	99±0.8	149±1.2	148±1.2	158±2.8	157±3.1
End point	100±0.9	93±0.9	98±2.4	92 ±2.6	150±1.6	142±1.8	159±5.5	154±4.9
Change	-1.9±0.7	-7.5±0.8	-1.8±2.5	-7.2±2.3	0.7±1.2	-6.3±1.4	1.2±4.5	-3.7±3.4
Double difference	-5.6		-5.4		-7.0		-4.9	

Response rate. The study report says the sponsor also performed a categorical analysis of the proportion of responders in each treatment group, using a Cochran-Mantel-Haenszel statistic, adjusting for center and subgroup interactions. These data are summarized in Table 8.

Table 8. Response rates (%) for change in sitting DBP (Study 124).

	Placebo N=18	Eprosartan N=119
Non-responders	79	58
End point <90 mmHg	16	36
End point 90-100 mmHg and 10 mmHg decrease	5.1	5.9

[5] Attributable to center 24.

1.5.3 Safety

Deaths. There were no deaths during or within 30 days of study participation.

Serious adverse events. Serious adverse events did not appear to be related to treatment. Seven adverse events met the sponsor's criteria for 'serious'. Serious or other adverse events associated with withdrawal are listed in Table 9. Other serious adverse events which did not lead to withdrawal were abdominal pain (placebo), thrombophlebitis, coagulopathy, and gastrointestinal hemorrhage (eprosartan; considered unlikely to be drug-related), severe asthenia (eprosartan; onset pre-dating treatment), and gastric ulcer hemorrhage (eprosartan; considered unlikely to be drug-related).

Table 9. Adverse events associated with withdrawal (Study 124).

ID	Age	Sex	Onset	Days	Event
Placebo					
124.001.00168	66	F	5	9	Cerebrovascular disorder, considered severe and unlikely to be drug-related.
124.002.00025	59	F	12	11	Headache, considered probably drug-related
124.009.00231	48	F	7	22	Generalized edema, considered not related.
124.011.00337	54	M	11	14	Headache, back pain, dyspnea, considered not related.
124.016.00295	67	M	42	42	Headache, considered unlikely drug-related.
124.020.00097	48	M	41	43	Chest pain, considered mild and probably drug-related.
124.022.00081	43	F	1	38	Anxiety, considered unlikely drug-related.
124.025.00376	64	F	15	28	Dyspnea and fatigue, both considered severe and possible drug-related.
124.030.00356	5	M	14	14	Pneumonia, considered unlikely drug-related.
Eprosartan					
124.020.00098	51	F	15	23	Headache and dizziness, considered mild and unlikely to be drug-related.
124.029.00278	68	F	39	39	Chest pain, considered mild and not drug-related.
124.034.00225	38	F	30	42	Asthenia, considered mild and possibly drug-related.

Common adverse events. Few adverse events bore any likely attribution to eprosartan. Fifty-two percent of subjects on placebo and 46% of subjects on eprosartan reported adverse events. Events occurring in more than 2 subjects in a treatment group and more common on eprosartan are listed in Table 10.

Table 10. Adverse events (%) more common on eprosartan (Study 124).

	Placebo N=120	Eprosartan N=123
Dizziness	1.7	5.7
Abdominal pain	2.5	3.3
Depression	1.7	2.4
Upper respiratory infection	5.0	5.7
Cough	0.8	4.1
Hematuria	0	2.4

Lab findings. There were small, clinically-insignificant changes in ECG intervals. Review of minima and maxima of lab values at baseline and on-treatment revealed no areas of concern.

1.6 Summary

Study 124 was conducted and submitted to support the use of eprosartan once daily for the treatment of mild-to-moderate hypertension. Other studies submitted with the original NDA were deemed inadequate for this purpose. Study 124 had about 4 times as many subjects per group as is usual, in anticipation of there being a relatively small treatment effect.

The conduct of Study 124 was marred by protocol violations at several sites and suspect data at the largest center. However, the study was large enough that the 7 centers with the largest observed treatment effects could be dropped from the analysis and still obtain $p<0.05$.

Most likely, the treatment effect seen here is real. The once-daily treatment effects of many antihypertensive agents are poorly predicted by the single-dose pharmacokinetics. This is probably another example of that poorly understood phenomenon.

Even if this assessment is incorrect, and eprosartan is ineffective when given once daily, little harm can be expected. The problem can be expected to sort itself out in the marketplace, as physicians discover they need more clinic visits to achieve the goals of treatment with eprosartan.

Standing blood pressures were not analyzed. Supine blood pressures were not recorded. Blood pressures near the time of peak effect were not obtained. At least for the first few doses, the trough-to-peak ratio can be expected to have been small, but only one subject on eprosartan discontinued for dizziness, and even that event does not sound like postural hypotension. Thus, if one believes the treatment effect is real, the predicted low trough-to-peak ratio should cause no safety concern.

Dr. Maryann Gordon deserves to be commended for detecting (by entirely independent means) irregularities in the data for center 24.